An Unusual Oxidation of Some 5α-Hydroxyandrost-2-enes

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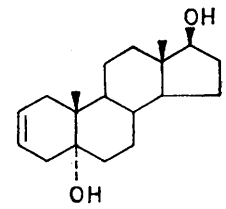
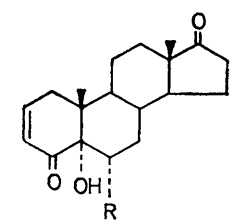
5α-Hydroxyandrost-2-enes are smoothly oxidized by 8N-chromium trioxide to 5α-hydroxyandrost-2-en-4-ones.

THE 8N-chromium trioxide reagent [1] is an efficient means of cleanly oxidizing secondary alcohols to ketones and it has been widely used in the steroid series.[2] Recently there have been reports [3] of the formation of epoxides from the oxidation of allylic axial alcohols; isolated double bonds are also occasionally attacked.[4]

Oxidation of 5α,17β-dihydroxyandrost-2-ene (1) [5] with 8N-chromium trioxide in acetone at room temperature for 1 h afforded a compound, $C_{19}H_{26}O_3$, $\nu_{max.}$ 3480, 1730, and 1675 cm^{-1}, $\lambda_{max.}$ 230 nm (ε 7100). Thus in addition to the hydroxy-group and 17-oxo-group, the molecule also contained an αβ-unsaturated ketone system, probably on ring A. The n.m.r. spectrum showed *C*-Me resonances at τ 9·12 and 9·05. Calculations based on Zurcher's tables [6] predict τ 9·07 and 8·76 for 5α-hydroxyandrost-2-ene-1,17-dione and τ 9·16 and 9·07 for 5α-hydroxyandrost-2-ene-4,17-dione. In the olefinic region the C-3 proton signal appeared as a double multiplet (τ 4·03; $J_{2,3}$ 10 Hz) and that of the C-2 pro[illegible] as an eight-line system (τ 3·17; *J* 10, 5, and 2 [illegible],



(1)



(2)

The couplings of 2 and 5 Hz are associated with the 1α- and 1β-protons. The C-3 proton signal also shows

[1] K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 1946, 39.

[2] P. Bladon, J. M. Fabian, H. B. Henbest, H. P. Koch, and G. W. Wood, *J. Chem. Soc.*, 1951, 2402; C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, 1956, **21**, 1547.

[3] E. Glotter, S. Greenfield, and D. Lavie, *J. Chem. Soc.* (*C*), 1968, 1646.

[4] P. S. Kalsi, K. S. Kumar, and M. S. Wadia, *Chem. and Ind.*, 1971, 31.

[5] P. D. Klimstra, U.S.P. 3,271,425 (*Chem. Abs.*, 1967, **66**, 11,122).

[6] R. F. Zurcher, *Helv. Chim. Acta*, 1963, **46**, 2054; N. S. Bhacca and D. H. Williams, 'Applications of N.M.R. Spectroscopy in Organic Chemistry,' Holden-Day, San Francisco, 1964, p. 19.

allylic couplings of 1 and 3 Hz, presumably to these protons. The unsaturated ketone was hydrogenated over palladised charcoal to give the known [7] 5α-hydroxyandrostane-4,17-dione. This showed *C*-Me resonances at τ 9·17 and 9·13 (Zurcher's tables [6] predict 9·17 and 9·12) and a solvent shift ($CDCl_3$ — C_6D_6) of +0·13 p.p.m., in agreement with results obtained in the cholestane series.[8] Consequently the oxidation had afforded 5α-hydroxyandrost-2-ene-4,17-dione (2; R = H). If the oxidation was carried out between 0 and 5° for ½ h, some 5α-hydroxyandrost-2-en-17-one could be isolated. Cholest-2-ene was not oxidized under these conditions. Hence this ready allylic oxidation requires a 5α-hydroxy-group, possibly to orient a chromate ester system close to the C-4 hydrogen atoms. In order to examine the possibility of steric hindrance by 6α-substituents, 6α-acetoxy-5α-hydroxyandrost-2-en-17-one was prepared.

3β-Methylsulphonyloxyandrost-5-en-17-one was treated with osmium tetroxide in pyridine to afford the corresponding 5α,6α-diol. The methanesulphonate group was then eliminated with collidine to give 5α,6α-dihydroxyandrost-2-en-17-one which was converted into its 6α-monoacetate with acetic anhydride in pyridine. However this was again smoothly oxidized to the corresponding αβ-unsaturated ketone, which showed spectral properties in accord with the structure (2; R = OAc). Hence this reaction affords an easy route to relatively inaccessible 4-oxo-5α-hydroxy-steroids.

The isomeric 5α,17β- and 5β,17β-dihydroxyandrost-3-enes both afforded androst-4-ene-3,17-dione on oxidation with 8N-chromium trioxide, thus reacting in a manner identical with that found [3] in the cholestane series.

EXPERIMENTAL

General details have been described previously.[9]

5α-Hydroxyandrost-2-ene-4,17-dione.—5α,17β-Dihydroxyandrost-2-ene [5] (1·72 g) dissolved in acetone (70 ml) was treated with 8N-chromium trioxide at room temperature for 1 h until the colour persisted. Methanol was added to discharge the colour, followed by sodium hydrogen carbonate. The mixture was filtered and extracted into ether; the extract was washed thoroughly with water, dried, and evaporated and the residue was chromatographed on alumina to afford *5α-hydroxyandrost-2-ene-4,17-dione* (1·37 g), which crystallized from acetone–light petroleum as needles, m.p. 215—217°, $[\alpha]_D^{20}$ +107° (*c* 0·76) (Found: C, 75·6; H, 8·3. $C_{19}H_{26}O_3$ requires C, 75·5; H, 8·8%); for spectra see Discussion section. By carrying out the oxidation in ice for ½ h variable amounts (20—50%) of 5α-hydroxyandrost-2-en-17-one (identified by its i.r. spectrum), accompanied by some starting material, were obtained. Cholest-2-ene was not oxidized under these conditions.

5α-Hydroxyandrostane-4,17-dione.— 5α-Hydroxyandrost-2-ene-4,17-dione (178 mg) in ethyl acetate (10 ml) was shaken for 4 h with 10% palladium–charcoal (100 mg) under hydrogen. The suspension was filtered through Celite. The Celite was washed with ethyl acetate and the combined filtrate and washings were evaporated to dryness. 5α-Hydroxyandrostane-4,17-dione (159 mg) was obtained as needles (from methylene chloride–methanol), m.p. 220—222°, $[\alpha]_D$ +175° (*c* 0·15), $\lambda_{max.}$ 296 nm (ε 70) {lit.,[7] m.p. 213—215°, $[\alpha]_D$ +168°, $\lambda_{max.}$ 296 (ε 82)} (Found: C, 74·7; H, 9·1. Calc. for $C_{19}H_{28}O_3$: C, 75·0; H, 9·3%), $\nu_{max.}$ 3490, 1745, and 1700 cm^{-1}, τ 9·17 (3H, s) and 9·13 (3H, s).

5α,6α-Dihydroxy-3β-methylsulphonyloxyandrostan-17-one.—3β-Methylsulphonoxyandrost-5-en-17-one (2·1 g) in pyridine (25 ml) was treated with osmium tetroxide (1·5 g) for 1½ h. Sodium hydrogen sulphite (3 g) in water (25 ml) was added, followed by a second portion of sodium hydrogen sulphite after a further ½ h. The *diol* (2·0 g) was filtered off and recrystallized from methanol to give needles, m.p. 158—160°, $[\alpha]_D$ +60° (*c* 0·5) (Found: C, 59·7; H, 8·1. $C_{20}H_{32}O_6S$ requires C, 60·0; H, 8·05%), $\nu_{max.}$ 3550, 3490, 3350br, and 1735 cm^{-1}, τ 9·08 (3H, s), 8·90 (3H, s), 6·95 (3H, s), and 6·30br (2H).

5α,6α-Dihydroxyandrost-2-en-17-one.—The above methanesulphonate (1·5 g) in collidine (10 ml) was heated under reflux for 1 h. The solution was cooled and poured into dilute hydrochloric acid, and the steroid was recovered in ethyl acetate. Chromatography on alumina in 50% ethyl acetate–light petroleum afforded *5α,6α-dihydroxyandrost-2-en-17-one* (1·1 g), which crystallized from acetone–light petroleum as prisms, m.p. 147—148°, $[\alpha]_D$ +11° (*c* 0·3) (Found: C, 74·7; H, 8·9. $C_{19}H_{28}O_3$ requires C, 75·0; H, 9·3%), $\nu_{max.}$ 3500, 3480br, 1735, and 1660 cm^{-1}, τ 9·15 (3H, s), 9·12 (3H, s), 6·40 (1H, m), and 4·30 (2H, m).

6α-Acetoxy-5α-hydroxyandrost-2-en-17-one was prepared with acetic anhydride in pyridine and had m.p. 197—199°, $[\alpha]_D$ +76° (*c* 0·5) (Found: C, 72·4; H, 8·7. $C_{21}H_{30}O_4$ requires C, 72·8; H, 8·7%), $\nu_{max.}$ 3500 and 1735 cm^{-1}, τ 9·15 (3H, s), 9·05 (3H, s), 7·95 (3H, s), 5·00 (1H, m), and 4·3 (2H, m).

Oxidation of 6α-Acetoxy-5α-hydroxyandrost-2-en-17-one.—The steroid (500 mg) in acetone (10 ml) was treated with 8N-chromium trioxide (1·5 ml) for 1 h at room temperature. Methanol was added, the solution was diluted with water, and the product was filtered off. *6α-Acetoxy-5α-hydroxyandrost-2-ene-4,17-dione* crystallized from acetone–light petroleum as needles, m.p. 189—192°, $[\alpha]_D$ +86° (*c* 0·5) (Found: C, 69·7; H, 7·8. $C_{21}H_{28}O_5$ requires C, 70·0; H, 7·8%), $\nu_{max.}$ 1745, 1735, and 1685 cm^{-1}, τ 9·12 (3H, s), 9·05 (3H, s), 7·90 (3H, s), 4·40 (1H, m), and 3·2 (1H, m).

Oxidation of 5α,17β- and 5β,17β-Dihydroxyandrost-3-enes.—The steroids (250 mg) in acetone (5 ml) were treated with 8N-chromium trioxide (0·5 ml) for 1 h at room temperature. Methanol was added, the solutions were diluted with water, and the products were recovered in ether. Chromatography on alumina afforded androst-4-ene-3,17-dione (120 and 140 mg, respectively), m.p. 172—173° (lit.,[10] 174°), identified by comparison of the i.r. spectra with that of an authentic sample.

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[7] R. Hanna, T. Rull, and G. Ourisson, *Bull. Soc. chim. France*, 1961, 1209.
[8] E. Glotter and D. Lavie, *J. Chem. Soc.* (*C*), 1967, 2298.
[9] J. R. Hanson and T. D. Organ, *J. Chem. Soc.* (*C*), 1970, 513.
[10] L. F. Fieser and M. Fieser, 'Steroids,' Reinhold, New York, 1959, p. 512.